Multifactorial Traits

Chapter Seven
Multifactorial

• Not all diseases are Mendelian
• Multifactorial = many factors

In Genetics:
• Multifactorial = both environment and genetics (usually more than one gene)
• Polygenic = more than one gene
• Each gene separately follows Mendel’s laws, but the trait overall does not
Complex Traits

• Disorder that is proven heritable, yet has no clear mode of inheritance
  – Doesn’t follow Mendel’s laws

• More than one gene - polygenic
• Interaction between genes - epistasis
• Interaction between genes and environment - multifactorial
Why Common Complex Disorders and Rare Mendelian Disorders?

• Evolution can act upon a single detrimental gene
  – negative selection

• Gene functions that are good for some things, but can be harmful in excess
  rational fear vs. anxiety disorders

• Normal alleles only predisposing
  – other mutations/environment present
Genes vs. Environment

Percent Genetic Control

Eye Color | Heart Disease | Car Accident

0 | 100 | 0
Genes vs. Environment

- Eye Color
- Heart Disease
- Car Accident
Causation

• There are only two factors that cause any trait:
  1. Genetics
  2. Environment

• **Nature vs. Nurture**

• Interaction of two is multifactorial
Multifactorial Traits:

- Height
- Weight
- Eye color
  - although basically no environmental component is involved
- Skin color
- Heart Disease
- What else?
Quantitative Traits

• Quantitative = measurable traits
• Disease state is Qualitative
  – Affected vs. unaffected
  – Show trait vs. do not show trait

  ex  Autistic or normal?

• Multifactorial traits are often Quantitative
  – Height ? – quantify in inches
  – Weight ? – quantify in pounds

  ex  “speaking ability is stuck at 2 years of age”
Quantitative Traits

- Quantitative traits produce a continuum of phenotypes:
Quantitative Traits

- Disease state may be beyond “threshold”
Quantitative Traits

Rather than genes people often talk about:

• Quantitative Trait Loci (QTL) = chromosomal regions that have been associated with a complex trait

• If a QTL is correct then one of the genes residing in this region should be directly involved in causing trait

Remember – More than one gene!

therefore – more than one QTL too
How to identify QTL

1. Linkage

2. Animal Models

3. Association Studies
QTL Mapping

• Start with a complex trait of interest
• Phenotype a large group of individuals for trait – quantitatively
• Genotype everyone

• Do people who share the trait also share specific genomic regions (QTL) more often than chance?
Wait a Second!?!?

• What if the trait we are interested in is NOT genetic at all?
• What would happen then?

• No matter how hard you studied, you would never find the genes, because there are none.
1st: Is Trait Genetic?

• Calculate Heritability

• Heritability ($H^2$) = proportion of the trait that is controlled by genetics
  – $H^2 = 100\%$ – trait is fully genetic
  – $H^2 = 0\%$ – trait is fully environmental

• Complex traits are somewhere in between
Heritability

• Different ways to calculate/estimate

• All based on this:

\[
\frac{\text{# of relatives that share the trait}}{\text{# expected to share if trait was 100% genetic}}
\]

• Expected is calculated based on amount of genetic material shared between two relatives
Heritability – Expected:

- Use “Correlation Coefficient”
- Fancy way of saying – how related are these two people?

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Percent Genes Shared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monozygotic Twins</td>
<td>100%</td>
</tr>
<tr>
<td>Dizygotic Twins</td>
<td>50%</td>
</tr>
<tr>
<td>Siblings</td>
<td>50%</td>
</tr>
<tr>
<td>Parent and Child</td>
<td>50%</td>
</tr>
<tr>
<td>Aunt or Uncle</td>
<td>25%</td>
</tr>
<tr>
<td>Grandparent</td>
<td>25%</td>
</tr>
<tr>
<td>First Cousin</td>
<td>12.5%</td>
</tr>
</tbody>
</table>
Heritability

• Gather a group of relatives
  – 100 sibling pairs
  – 100 MZ twins

• Phenotype for trait:
  
  \[ \frac{40}{100} = 80\% \]
  
  Therefore, trait is 80 % controlled by genetics
  
  – 20 % controlled by environment
Problems with Heritability?

What do you think is wrong, or lacking, with $H^2$ estimate from relative pairs?

1. Families share genetics AND environment
2. More shared genetics usually correlates to more shared environment too:
   - *example* Twins usually share bedroom
   - Siblings raised in same house, unlike cousins
Separate Genes from Environment

1. Adopted children
   - Compare birth parents to adopted parents
   - Sharing environment only, not genes

2. Twins
   - Compare MZ vs. DZ twins
   - Differences in twins is only difference between amount of genes shared, environment is constant
Concordance Rates

• Compare the percent of MZ twins that are concordant for the trait vs. the percent of DZ twins concordant

• If MZ twins are more concordant than difference is attributed to genetics

  ex  Autism:  90% MZ vs.  2% DZ
  Homosexuality:  52% MZ vs.  20% DZ
  Depression:    46% MZ vs.  9% DZ
Problem with Concordance?

More shared genetics usually correlates to more shared environment too
  – MZ twins can be raised in more similar environments than DZ twins

\(\text{ex}\) Tuberculosis was found more often in MZ twins than DZ twins
  – Obviously TB (caused by bacteria), is not genetic at all!
What would be ideal?

- MZ twins, separated at birth, raised completely apart

- Animal models, where one can separate the genetics from the environment
Genetic Counselors

• What happens when parents ask you the risk of having a child with a complex disorder?

• Cannot calculate an exact statistical likelihood based on Mendel’s laws

Instead give:

• Heritability estimates

• Empiric Risk
Empiric Risk

• The incidence of the trait in a specific population:

  Differs based on ethnic background:

<table>
<thead>
<tr>
<th>Ethnic Background</th>
<th>Prevalence of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>50</td>
</tr>
<tr>
<td>African</td>
<td>3.8</td>
</tr>
<tr>
<td>African-American</td>
<td>26</td>
</tr>
<tr>
<td>Native American</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Also depending on whether relative has trait:

<table>
<thead>
<tr>
<th>Relationship to Affected Individual</th>
<th>Risk of Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identical Twin</td>
<td>40%</td>
</tr>
<tr>
<td>Sibling</td>
<td>5%</td>
</tr>
<tr>
<td>Child</td>
<td>3.5%</td>
</tr>
<tr>
<td>First Cousin</td>
<td>0.30%</td>
</tr>
</tbody>
</table>
QTL Mapping

• Start with a complex trait of interest
  – That shows strong genetic contribution
• Phenotype a large group of individuals for trait – quantitatively
• Genotype everyone

• Do people who share the trait also share specific genomic regions (QTL) more often than chance?
QTL Mapping

1. Linkage:
   - Marker and phenotype are correlated

2. Animal Models
   - Animal can be manipulated to show phenotype
   - Compare differences in genetics, matched to differences in phenotypes

3. Association Studies:
   - Are certain alleles correlated with phenotype?
Association Studies

“Linkage Disequilibrium” – alleles are inherited together (rather than genes)
  – LD only ranges a short distance
  – ~ 10,000 bases
  – Because alleles are so close they are always inherited together (no crossing over)

• Association comparing alleles
• Linkage usually done in families, association usually done case vs. control
Case vs. Control

• Gather a group of individuals with trait
• Compare them to a group of individuals who do not have trait
• Whatever alleles (genes) are different = cause of trait
• Problems?
  – What about ethnic genetic background?
  – Need to perfectly match the background of the two groups
Case vs. Control

• Perfect match = family members
  Association studies are now often done in:
  – Sib pairs (two siblings, both affected)
  – Trios (two parents and one affected child)

• 2\textsuperscript{nd} best = genotype both groups across entire genome
  – Make sure genetic backgrounds are the same
  – “Genomic Controls”
Complexity of Trait

• More complex the trait, more difficult it will be to identify QTL or genes involved

This is assuming environment is completely controlled for
Summary

1. Figure out whether trait is genetic:
   - Compare relatives vs. general population
   - MZ vs. DZ twins
   - Adoption Studies

2. Estimate how genetic:
   - Heritability
   - Empiric Risk

3. Try to identify genes involved in trait (QTL’s)
Summary

QTL = regions associated with phenotype:

- Linkage – correlation between genomic regions and phenotype
- Association – correlation between alleles and phenotype
- Animal Models

• Association Studies can be:
  - Case vs. Control
  - Sib pairs or Trios
Important Terms:

Empiric Risk – known incidence of trait in particular population

Heritability – estimate of percentage of trait that is caused by genetics

Correlation Coefficient – proportion of genes two relatives share

Concordance – Percentage of twin pairs that both show phenotype
Example: Obesity

• Qualitative = obese, overweight, normal
• Quantitative = weight in pounds
• Multifactorial
  – Controlled by environment
  – Controlled by genetics:

<table>
<thead>
<tr>
<th>Protein</th>
<th>Effect on Appetite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>↓</td>
</tr>
<tr>
<td>Leptin transporter</td>
<td>↓</td>
</tr>
<tr>
<td>Leptin receptor</td>
<td>↓</td>
</tr>
<tr>
<td>Neuropeptide Y</td>
<td>↑</td>
</tr>
<tr>
<td>Melanocortin-4 receptor</td>
<td>↓</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>↑</td>
</tr>
<tr>
<td>PYY</td>
<td>↓</td>
</tr>
</tbody>
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Next Class:

• Read Chapter Eight

• Homework – Chapter Seven Problems;
  – Review: 1, 4, 7, 8, 10
  – Applied: 1, 3, 5, 6, 10, 11